Remarks

Prior to entry of this amendment, claims 1-38 and 47 were pending in the application. Claims 2, 6-8 and 20 have been canceled. Applicants expressly reserve the right to pursue protection of any or all of the canceled subject matter in one or more continuing applications. Claims 1 and 4-5 and 21-22 have been amended. Support for the amendment of claim 1, 4 and 21-22 can be found throughout the specification, such as on page 9, lines 14-26. Claim 1 is also amended herein to incorporate the limitations of claim 2. Claim 5 is amended herein to correct form.

Applicants believe no new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1, 3-5, 9-38 and 47 are pending in this application**. Reconsideration of the pending claims is requested.

Restriction Requirement

The Office action alleges that there is no special technical feature, as the '846 publication teaches the treatment of SLE with uteroglobin. The Office action alleges that the present application defines SLE as an IgA mediated disorder on page 2. This allegation is incorrect. The paragraph that bridges pages 1-2 of the specification is part of the background section that describes glomerulopathies, which includes the pathology of SLE (see the top of page 2). The next paragraph of the background section delineates IgA mediated glomerulopathy as one type of golmerulopathy (see page 2, lines 6-24). Applicants believe that the specification clearly describes glomerulopathies, and clearly delineates SLE glomerulopathy from an IgA mediated disorder. In fact, *SLE is known to be associated with an IgA deficiency* (see Rankin and Isenberg, Lupus 6: 390-4, 1997, copy of the abstract enclosed as Exhibit A). Reconsideration is respectfully requested. Applicants expressly reserve the right to petition the restriction requirement.

Priority Claim and Information Disclosure Statements (IDS)

Applicants thank the Examiner for acknowledging the priority claim. Applicants thank the Examiner for considering the three IDS's submitted in the present application.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-8, 18-23 and 47 are rejected under 35 U.S.C. § 112, first paragraph as allegedly the specification does not provide enablement for a method of treating or preventing an IgA mediated disorder using uteroglobin, or a fragment, derivative or mimetic thereof. Claims 2, 6-8 and 20 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this rejection as applied to the claims 1, 18-19, 21-23 and 47 as amended. The specification provides sufficient guidance for the claimed methods that use fragments of uteroglobin that retain the biological function of uteroglobin. This is exemplified by the following Wands analysis:

1. The breadth of the claims

The claims are limited to methods of treating IgA mediated disorders, such as IgA mediated nephropathy using uteroglobin or a fragment thereof that retains the biological function of uteroglobin.

2. The nature of the invention

The invention is limited to therapeutic methods for treating IgA mediated disorders in subjects by administering uteroglobin or a fragment thereof that retains the biological function of uteroglobin.

3. The state of the prior art

The prior art teaches the amino acid sequence of uteroglobin and its biological function (see the specification at page 1, lines 9-26). Fragments and derivatives of uteroglobin that retain the biological function of uteroglobin are described in the specification and are known in the art (see for example, U.S. Patent No. 5,266,562 and Miele et al., Nature 335: 726-730, 1988, submitted herewith as Exhibit B and Exhibit C, respectively). The purification of uteroglobin and fragments thereof is known in the art (see for example, column 3 of U.S. Patent No. 5,266,562 and the specification at page 38, line 13 to page 42, line 2). Procedures and formulations for the administration of polypeptides are known in the art (for example, see the specification page 47, line 7 to page 48, line 26 and column 8 of U.S. Patent No. 5,266,562).

4. The level of skill of one of ordinary skill in the art

The level of skill of the average molecular biologist or immunologist is high.

5. The level of predictability in the art

Uteroglobin fragments that retain the biological function of uteroglobin are known in the art and are described in the specification. The administration of polypeptides is routine to a skilled clinician.

6. The amount of direction provided in the application

There is considerable direction provided in the application. The amino acid sequence of uteroglobin is provided (see, for example, Fig. 1 and SEQ ID NOs: 1-4). Pharmaceutical compositions are described (see the specification at pages 47-48). Fragments uteroglobin that retain the biological function are described (see, for example, page 9, lines 1-26). Screening methods to identify fragments of use are provided, such as on page 3, lines 26-31. Ten exemplary polypeptides with the biological activity of uteroglobin are disclosed on page 35, lines 1-10.

7. The existence of working examples

SEQ ID NOs: 1-4 are provided in the specification. Results are presented in a transgenic mouse model that document that IgA is deposited in the glomeruli in mice that do not express uteroglobin; IgA is not deposited in the glomeruli of mice that express uteroglobin (see pages 21, line 26 to page 22, line 10). Moreover, mice deficient for the production of uteroglobin (uteroglobin knockout mice) manifest pathological features of IgA nephropathy. Ten polypeptides that have the biological activity of uteroglobin are disclosed on page 35, lines 1-10.

Experimental results are presented in an *in vivo* model that document that uteroglobin interferes with the binding of IgA and fibronectin, thereby averting glomerular deposition of both IgA and fibronectin in vivo (see Example 6, pages 25-27).

Thus, working examples are provided.

8. The quantity of experimentation needed to make or use the invention.

Synthetic polypeptides can be produced by automated machinery. In addition, a number of expression vectors are known in the art (and commercially available) that can be used to produce the claimed polypeptides. Thus, only very limited routine experimentation is required to produce uteroglobin and fragments and derivatives thereof that retain the biological function of uteroglobin. Methods for delivery of pharmaceutical agents to a subject are well known to a skilled clinician. Thus, very little experimentation is required to practice the claimed methods.

Claims 1-8, 18-23 and 47 are rejected under 35 U.S.C. § 112, first paragraph as allegedly there is insufficient written description for uteroglobin fragments, derivatives and mimetics. Claims 2-3, 6-8 and 20 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to claims 1, 4-5, 18-19, 21-23 and 47 as amended.

MPEP 2163.02 states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

The specification clearly describes fragments of uteroglobin that retain the biological function (see, for example, page 9, lines 1-26, Fig. 1, and SEQ ID NOs: 1-4). The biological function of uteroglobin is also described (see, for example, page 1, lines 16-18). Methods for producing uteroglobin and fragments thereof are also described (see the specification at page 38, lines 13 to page 42, line 2). Polypeptides are disclosed that have the biological function of uteroglobin (SEQ ID NOs: 18-27).

Applicants submit that given the ample guidance provided by the specification, one of skill in the art can readily identify practice the claimed methods with a uteroglobin or a fragment thereof that retains the biological function of uteroglobin.

> *(Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("In claims involving chemical materials, generic formulae usually indicate with specificity what the generic

> claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.").

Uteroglobin inhibits inflammation (see column 1, lines 5-10). Specifically uteroglobin inhibits erythema and induration induced by phorbol myristate acetate (see column 6, lines 60-67). In the present application, exemplary uteroglobin fragments of use are disclosed in the specification (see page 9, lines 20-26). Methods that identify uteroglobin fragments of use are also provided (see the specification at page 3, line 26 to page 4, line 3.

Thus, there clearly is sufficient written description for the claimed methods. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection Under 35 U.S.C. § 102

Claims 1-8, 18-23 and 47 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by PCT Publication NO. WO 98/58346 (hereinafter "the '346 publication"), as evidenced by the specification on pages 2-3. Claims 1-8, 18-23 and 47 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,255,281 (hereinafter "the '281 patent"). Claims 2, 6-8 and 20 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with these rejections as applied to claims 1, 4-5, 18-19, 21-23 and 47 as amended.

The '346 publication claims priority to U.S. Patent Application No. 08/864,357, which issued as the '281 patent. Thus, the specification (although not the claims) of the '346 publication is identical to the specification of the '281 patent.

The specification at pages 2-3 is discussed above. Specifically, the specification describes glomerulopathies. The specification discloses that one type of glomerulopathy is IgA-mediated glomerulonephritis. However, the specification clearly delineates IgA-mediated glomeronephritis from other disorders associated with a glomerulopathy, such as SLE.

The '346 publication and the '281 patent disclose the use of uteroglobin to treat inflammatory conditions and fibrotic conditions. It is disclosed that uteroglobin is of use to treat some autoimmune diseases (page 12), including bronchial asthma (page 3). It is further disclosed that nephropathy (page 17) and acute renal failure due to diabetic nephropathy and idiopathic nephropathy (page 18) are "candidates" for treatment or prevention by uteroglobin.

As noted in the specification on pages 2-3, glomerulonephritis is a diverse group of diseases that damage the glomerulus. Glomerulonephritis includes poststreptococcal glomerulonephritis, rapidly progressive glomerulonephritis, minimal change disease, focal glomerulonephritis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, Goodpasture's syndrome, systemic lupus erythematosis, Wegener's granulomatosis, autoimmune thrombocytopenic purpura, and Henoch-Schoenlein purpura.

IgA mediated nephropathy or Berger's disease is one specific type of nephropathy. IgA mediated nephropathy is a clinical/pathological entity defined by the presence of macroscopic or microscopic hematuria and mesangial IgA deposits mainly in the mesangium of the glomerular tuft of the kidney, which normally filter wastes and excess water from the blood. The IgA protein prevents this filtering process. In the U.S., the incidence of this disease is approximately 4% of all renal biopsies. Treatments of use for other types of neuropathy, are not efficacious in treating IgA-mediated neuropathy.

Bronchial asthma is an IgE mediated disorder (and is discussed in the '346 publication and the '281 patent), while Goodpasture's syndrome is an IgA-mediated disorder associated with dyspnea that is clinically diagnosed by the presence of IgA mediated nephropathy in association with other clinical findings. Goodpasture's syndrome is characterized by IgA mediated deposits in the lung aveoli and in the glomeruli, arising from elevated levels of IgA. Similarly, Wegener's granulomatosus is a disorder of the upper respiratory tract that is associated with IgA deposits in the kidneys. Goodpasture's disease and Wegener's granulomatosus are very different disease entities than bronchial asthma.

It is solely the present disclosure that teaches that uteroglobin can be used to treat disease associated with increased IgA, such as IgA nephropathy, which accounts for only a subset of glomerulonephritis. In addition, it is solely the present specification that discloses that uteroglobulin can be used to treat pulmonary disorders associated with increased IgA, such as Goodpasture's disease. Thus, the general teachings of the '346 publication and the '281 patent do not suggest, nor render obvious, the selection of a subject with an IgA mediated disorder. In addition, neither the '346 publication nor the '281 patent teach the use of uteroglobin to treat a subset of individuals affected with IgA mediated autoimmune disease (such as those individuals

with IgA mediated nephropathy). It is only the teachings of the present specification that provides this insight.

In view of the amendments to the claims and the remarks presented herein, reconsideration and withdrawal of the rejection are respectfully requested.

Request for Interview

If an additional rejection is asserted, or if the present rejections are maintained, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Conclusion

It is respectfully submitted that the present claims are in a condition for allowance. Should the Examiner have further questions or comments with respect to examination of this case, it is respectfully requested that the Examiner telephone the undersigned so that further examination of this application can be expedited.

Respectfully submitted,

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